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(71) Applicants (*for all designated States except US*): SMITHKLINE BEECHAM PLC. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). SMITHKLINE BEECHAM FARMACEUTICI S.P.A. [IT/IT]; Via Zambeletti, I-20021 Baranzate (IT).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): ARCH, Jonathan, Robert, Sanders [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). CLARKE, Geoffrey, Douglas [GB/IT]; SmithKline Beecham Farmaceutici S.A., Via Zambeletti, I-20021 Baranzate (IT).

(74) Agent: RUSSELL, Brian, John; SmithKline Beecham, Corporate Intellectual Property, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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(54) Title: USE OF POTASSIUM CHANNEL ACTIVATORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF PAIN

(57) Abstract

A method for the treatment of pain in mammals, which comprises administering to the mammal in need of such treatment an effective amount of a potassium channel activator.

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# USE OF POTASSIUM ACTIVATORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATEMENT OF PAIN.

The present invention relates to a method for the treatment of pain in mammals.

EP-A-76075, 91748, 93535, 95316, 107423, 120426, 120427, 126311, 126350, 126367, 138134, 139992, 168619, 205292, 214818, 250077, 321175, 359537, 375449, 426379, 431741, WO 89/05808 and WO 91/11446 (Beecham Group p.l.c.) describe classes of compounds which are believed to be potassium channel activator antihypertensive agents.

U.K. Patent No. 1489879 discloses the compound N"-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine and, in Example 47, a process by which it can be prepared. The compound, which is referred to herein by its common name, pinacidil, is described in the patent as a hypotensive compound. In "Drugs of the Future" Vol. VI(3), 149, 1981, pinacidil is described as a vasodilator. It is now known that pinacidil is a potassium channel activator.

EP-A-112776 (Rhône-Poulenc Santé) discloses the compound N-methyl-2-(3-pyridinyl)tetrahydrothiopyran- 2-carbothioamide-1-oxide, which is known as RP 49356 (and includes its active enantiomer, aprikalim, and is a potassium channel activator antihypertensive agent.

Other compounds currently being developed for use as potassium channel activators include RO-316930 (Roche), SDZ-PCO-400 (Sandoz), WAY 120491 (Wyeth-Ayerst) and HOE-234 (Hoechst).

EP-A-0 350 805 (Biersdorf), EP-A-0 277 611, EP-A-0 277612, EP-A-0 337 179, and EP-A-0 355 565 (Hoechst Aktiengesellschaft) EP-A-0 415 065 (E.Merck), EP-A-0-450 415 (Squibb), EP-A-0-466 131 (Nissan Chemical Industries Ltd), EP-A-0339562 (Yoshitomi Pharmaceuticals), EP-A-0 360 621 (Ortho Pharmaceuticals), EP-A 0 489 300 (Uriach), DE 3,831,697 (Hoechst), EP-A 0 432 893 (Yamanouchi), DE 4,010,488 (Hoechst), EP-A-0482934, EP-A-0296975, JO-2004-791, EP-A 0571822, WO\92\02514, WO\89\11477 and WO\89\07103 also describe certain compounds which are believed to possess anti-hypertensive activity.

EP-A-0 430 621 and EP-A-0 385 584 (Beecham Group plc) describe the resolution of certain intermediates useful in the preparation of the compounds described in the above mentioned patent applications.

EP-A-0 194 885 (E. Lilly) describes certain amino substituted benzopyran derivatives possessing anti-convulsant activity.

EP-A-0509-762 (E.R. Squibb) describes certain indole and dihydroquinoline substituted derivatives which as disclosed as possessing *inter alia* anti-hypertensive activity.

EP-A-314446 (American Home Products Corporation), EP-A-296975 and 312432 (Sanofi), EP-A-298452 (F. Hoffmann-La Roche and Co.), EP-A-273262, EP-A-308972 and 340718 (Merck Patent GmbH), EP-A-339562 (Yoshitomi Pharmaceutical Industries Ltd.), GB 2204868A (Sandoz Limited), EP-A-365416 (Adir and Co), EP-A-344747 (Fujisawa), and EP-A-326297 (Rhone-Poulenc) describe classes of benzopyran derivatives which are believed to be potassium channel activator antihypertensive agents.

It has now been discovered that compounds of these classes have analgesic properties and are of potential use in the treatment of pain in mammals.

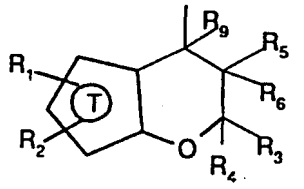
Accordingly, the present invention provides a method for the treatment of pain in mammals, such as humans, which method comprises administering to the mammal in need of such treatment an effective amount of a potassium channel activator, such as a compound of formula (I), or a pharmaceutically acceptable salt thereof:


(I)

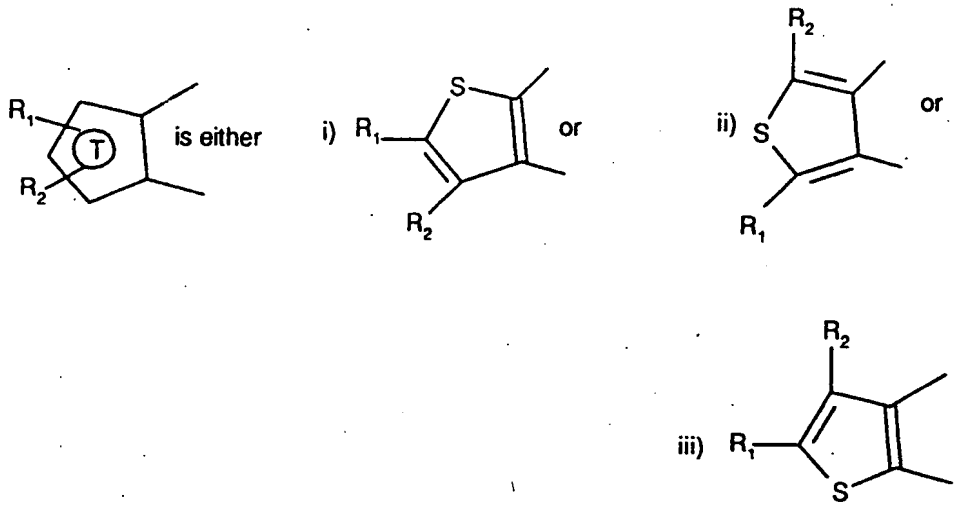
wherein:

P is a ring system selected from the following:

a)

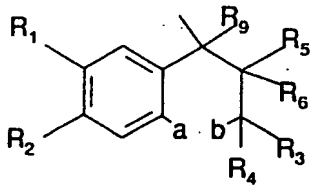



wherein;

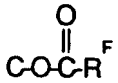



and the other variables are as defined below:

b)

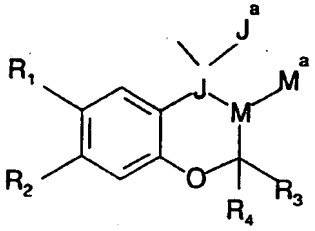



in which either a and b together represent a bond or $CH_2$ or a and b together represent a carbonyl group, a group $C{=}NOR^F$, $CHOR^F$ or




where $R^F$ is hydrogen or $C_{1-6}$ alkyl; or

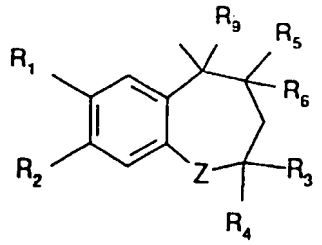
c)




in which either J is nitrogen and $J^a$ is a lone pair of electrons, M is carbon and $M^a$ is $R_5$; or

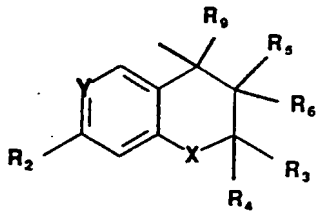
J is carbon and M is nitrogen and $J^a$ and $M^a$ are hydrogen; or

d)



in which Z is oxygen or $CH_2$;

e)



in which X is oxygen or NR in which R is hydrogen or $C_{1-4}$ alkyl; Y is nitrogen and $R_2$ is hydrogen or Y is C-$R_1$;

and;

where:

either one of $R_1$ and $R_2$ is hydrogen and the other is selected from the class of hydrogen, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyl optionally interrupted by oxygen or substituted by hydroxy, $C_{1-6}$ alkoxy or substituted aminocarbonyl, $C_{1-6}$ alkylcarbonyl, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ alkylcarbonyloxy, $C_{1-6}$ alkoxy, nitro, cyano, halo, trifluoromethyl, $CF_3S$, or a group $CF_3$-A-, where A is -$CF_2$-, -CO-, -$CH_2$-, CH(OH), $SO_2$, SO, $CH_2$-O, or CONH, or a group $CF_2H$-A'- where A' is oxygen, sulphur, SO, $SO_2$, $CF_2$ or CFH; trifluoromethoxy, $C_{1-6}$ alkylsulphinyl, perfluoro $C_{2-6}$ alkylsulphonyl, $C_{1-6}$ alkylsulphonyl, $C_{1-6}$ alkoxysulphinyl, $C_{1-6}$ alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, phosphono, arylcarbonyloxy, heteroarylcarbonyloxy, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, $C_{1-6}$ alkylcarbonylamino, $C_{1-6}$ alkoxycarbonylamino, $C_{1-6}$ alkyl-thiocarbonyl, $C_{1-6}$ alkoxy-thiocarbonyl, $C_{1-6}$ alkyl-thiocarbonyloxy, 1-mercapto $C_{2-7}$ alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two $C_{1-6}$ alkyl groups, or $C_{1-6}$ alkylsulphinylamino, $C_{1-6}$ alkylsulphonylamino,$C_{1-6}$ alkoxysulphinylamino or $C_{1-6}$ alkoxysulphonylamino, or ethylenyl terminally substituted by $C_{1-6}$ alkylcarbonyl,

nitro or cyano, or -C($C_{1-6}$ alkyl)NOH or -C($C_{1-6}$ alkyl)$NNH_2$, or one of $R_1$ and $R_2$ is nitro, cyano or $C_{1-3}$ alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two $C_{1-6}$ alkyl or by $C_{2-7}$ alkanoyl; or where possible $R_1$ and $R_2$ when adjacent together are -$(CH_2)_4$- or -CH = CH-CH = CH-, or form an optionally substituted triazole or oxadiazole ring;

one of $R_3$ and $R_4$ is hydrogen or $C_{1-4}$ alkyl and the other is $C_{1-4}$ alkyl, $CF_3$ or $CH_2X^a$ where $X^a$ is fluoro, chloro, bromo, iodo, $C_{1-4}$ alkoxy, hydroxy, $C_{1-4}$ alkylcarbonyloxy, -S-$C_{1-4}$ alkyl, nitro, amino optionally substituted by one or two $C_{1-4}$ alkyl groups; cyano or $C_{1-4}$ alkoxycarbonyl or $R_3$ and $R_4$ together are $C_{2-5}$ polymethylene optionally substituted by $C_{1-4}$ alkyl;

$R_5$ is $C_{1-6}$ alkylcarbonyloxy, benzoyloxy, $ONO_2$, benzyloxy, phenyloxy or $C_{1-6}$ alkoxy and $R_6$ and $R_9$ are hydrogen or $R_5$ is hydroxy and $R_6$ is hydrogen or $C_{1-2}$ alkyl and $R_9$ is hydrogen or $R_5$ together with $R_9$ represents a bond and $R_6$ is hydrogen or $R_6$ and $R_9$ represents a bond and $R_5$ is hydroxy;

$R_7$ is a group of structure i):

(i)

wherein

either X is oxygen or sulphur; and

$R_7'$ is hydrogen, $C_{1-6}$ alkyl optionally substituted by hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl or carboxy, $C_{1-6}$ alkyl substituted by halogen, or $C_{2-6}$ alkenyl; aryl or heteroaryl either being optionally substituted by one or more groups or atoms selected from the class of $CF_3$, $CF_3O$-, $C_{1-6}$ alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, $C_{1-12}$ carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two $C_{1-6}$ alkyl groups; and

$R_8$ is hydrogen, $C_{1-6}$ alkyl, or a group $OR_p$ or $NHCOR_q$ wherein $R_p$ is hydrogen, $C_{1-6}$ alkyl, aralkyl, $C_{1-7}$ alkanoyl or aroyl and $R_q$ is as defined above for $R_7'$; or $R_7$ and $R_8$ are joined together to form $C_{3-4}$ polymethylene optionally substituted by one or two $C_{1-6}$ alkyl groups or hydroxy $C_{1-6}$ alkyl, or -$CH_2$-$(CH_2)_n$-Z-$(CH_2)_m$- wherein m and n are integers 0 to 2 such that m+n is 1 or 2 and Z is oxygen, sulphur or $NR_9$ wherein $R_9$ is hydrogen, $C_{1-9}$ alkyl, $C_{2-7}$ alkanoyl, phenyl $C_{1-4}$ alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy or halogen; mono- or bi-cyclic heteroarylcarbonyl; or $R_7$ and $R_8$ are joined to form -$B^1$=$B^2$-$B^3$=$B^4$-.

wherein one of $B^1$ to $B^4$ is $CR_r$ or N and the other three are $CR_r$ wherein $R_r$ is hydrogen or $C_{1-6}$ alkyl;

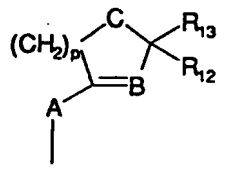
or X is N-CN, $N-NO_2$, $N-COR_{10}$ or $N-SO_2R_{10}$ wherein $R_{10}$ is $C_{1-3}$ alkyl, $NH_2$, $NH(C_{1-3}$ alkyl), $CF_3$ or phenyl optionally substituted as defined for $R_x$; and

$R_7'$ is $NHR_{11}$ wherein $R_{11}$ is hydrogen, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl; and

$R_8$ is hydrogen or $C_{1-6}$ alkyl; or

$R_7'$ and $R_8$ together are $C_{2-4}$ polymethylene;

or $R_7$ is a group of structure ii):




(ii)

wherein

A is O or $NR_{14}$ wherein $R_{14}$ is hydrogen, $C_{1-4}$ alkyl, formyl, acetyl or hydroxymethyl;

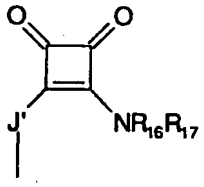
B is N or $CR_{15}$ wherein $R_{15}$ is hydrogen, halogen, formyl or hydroxymethyl;

C is $CH_2$, O, S, CH-Halogen, amino or $C_{1-6}$ alkylamino;

p is 1, 2 or 3; and

$R_{12}$ and $R_{13}$ are independently hydrogen or methyl or together are oxo- or thia-;

or $R_7$ is a group of structure iii)

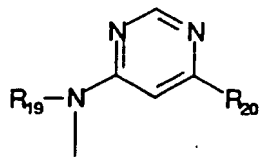



(iii)

wherein

J' is O or $NR_{18}$ wherein $R_{18}$ is hydrogen or $C_{1-6}$ alkyl, and $R_{16}$ and $R_{17}$ are independently hydrogen, $C_{1-6}$ alkyl, or (when $R_{16}$ is hydrogen) then $R_{17}$ is allyl, propargyl or $C_{3-6}$ cycloalkyl;

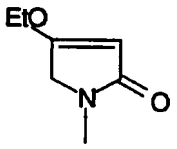
or $R_7$ is a group of structure iv)



(iv)

wherein

$R_{19}$ is hydrogen or $C_{1-6}$ alkyl; and $R_{20}$ is halo, amino or methylamino;
or $R_7$ is, or formula v);



(v)

or $R_7$ is tetrahydroisoquinolinone, 2,3-dihydro-1H- isoindol-1-one, 2-pyridine N-oxide, 2-hydroxyphenyl or 2-hydroxypyridine (all four possible isomers);
the $R_7$ moiety being cis or trans to the $R_5$ group when $R_5$ is other than hydrogen or a bond.

Suitable and preferred values for the variable groups or atoms in formula (I) are as described for the corresponding variables in the above-mentioned patents, the subject matter of which is incorporated herein by reference. It should be appreciated that further groups $R_7$, which are incorporated herein by reference are described in WO\92\02514 orSA\91\5891 and EP-571822.

All $C_{1-6}$ alkyl or alkyl containing groups in formula (I) are preferably selected from methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl.

$C_{3-8}$ cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl includes phenyl and naphthyl.

Heteroaryl includes a 5- or 6- membered monocyclic or 9- or 10- membered bicyclic of which 5- or 6- memebered monocyclic heteroaryl is preferred. In addition, 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl preferably contains one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur and which, in the case of there being more than one heteroatom, are the same or different. Examples of 5- or 6-membered monocyclic heteroaryl containing one, two or three heteroatoms which are selected from the class

of oxygen, nitrogen and sulphur include furyl, thienyl, pyrryl, oxazolyl, thiazolyl, imidazolyl and thiadiazolyl, and pyridyl, pyridazyl, pyrimidyl, pyrazolyl and triazolyl. Preferred examples of such groups include furanyl, thienyl, pyrryl and pyridyl, in particular 2- and 3-furyl, 2- and 3-pyrryl, 2- and 3-thienyl, and 2-, 3- and 4-pyridyl. Examples of 9- or 10-membered bicyclic heteroaryl containing one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur include benzofuranyl, benzothienyl, indolyl and indazolyl, quinolyl and isoquinolyl, and quinazolyl. Preferred examples of such groups include 2- and 3-benzofuryl, 2- and 3-benzothienyl, and 2- and 3-indolyl, and 2- and 3-quinolyl.

Suitable examples of groups or atoms for optional substitution of aryl and heteroaryl include one, two or three substituents independently selected from $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halo (such as fluoro, chloro, bromo), hydroxy, nitro and cyano.

Acyl groups are preferably carboxylic acyl, usually alkanoyl.

Preferably P is selected from e). Y is preferably nitrogen and $R_2$ is hydrogen or Y is C-$R_1$ where $R_1$ is preferably cyano and $R_2$ is hydrogen. $R_3$ and $R_4$ are preferably both methyl; $R_5$ is preferably hydroxy and $R_6$ and $R_9$ are hydrogen. X is preferably oxygen. $R_7$ is preferably selected from group i); $R_7$ is most preferably 2-oxo-1-pyrrolidinyl, or 2-oxo-1-piperidinyl.

Other examples of compounds believed to be potassium channel activators are described in U.K. Patent No. 1489879 (E. Lilly) which in particular describes, in example 1, the t-butyl analogue of pinacidil known as P1060, EP-A-350805 (Beiersdorf), EP-A-365416 (Adir), EP-A-344747 (Fujisawa), EP-A-360621 (Ortho Pharmaceutical Corp.), EP-A-355565 (Hoechst AKliengesellschaft), EP-A-363883 (Merck Patent GmbH)), EP-A-354553 (E.R. Squibb and Sons Inc.) and EP-A-375449 and European Patent Application No. 90305690.1 (Beecham Group p.l.c.), the subject matter of which are incorporated herein by reference.

A particularly preferred compound of formula (I) is the compound of Example 3 of EP-A-205292, (±)*trans*-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-2H-pyrano[3,2-c]pyridin-3-ol.

Another particularly preferred compound of formula (I) is the compound of Example 1 of EP-A-76075 and United States Patent No. 4446113, (±)-6-cyano-3,4-dihydro-2,2-dimethyl-*trans*-4-(2-oxo-1-pyrrolidinyl)-2H-benzo[b]pyran-3-ol, also known as cromakalim; and its (-)-enantiomer, also known as levcromakalim, disclosed in EP-A-120428.

Other particularly preferred potassium channel activators include RO 316930, SDZ PCO-400, WAY-120491, HOE-234, HOE-231, S-0121, FR 119748, EMD 57283, YM 934, NIP-121, RWJ-29009, BRL 55834, BDF 9333, U-89, 232,

KP294, SR 47063, Y27152, Y26763, UR 8225, KC-399, LP805, KRN 2391 and nicorandil.

Examples of pharmaceutically acceptable salts are as described in the aforementioned European Patent references, the subject matter of which are incorporated herein by reference.

Information with respect to structure and activity of the specific compounds listed hereinbefore may be obtained from well known pharmaceutical industry references, such as "Pharmaprojects", PJB publications Limited, Richmond, Surrey, U.K.

References to a potassium channel activator, including pinacidil or a compound of formula (I) and salts thereof, include solvates such as hydrates.

Potassium channel activators may be identified by standard methods, such as those described in EP-A-176689.

The compounds of formula (I), and salts thereof may be prepared as described in the aforementioned Patent Publications/References.

Preferably, a compound of formula (I) is in substantially pure pharmaceutically acceptable form.

Examples of the compounds of formula (I) include the examples described in the aforementioned Patent Publications/References.

It will be appreciated that the benzopyran compounds of formula (I) wherein $R_5$ is hydroxy, alkoxy, acyloxy or $ONO_2$ and/or wherein J is $C_{1-6}$ alkyl have an asymmetric centre at the 3- and 4- carbon atoms, and are capable of existing in the (3R, 4S), (3S, 4R), (3R, 4R) and (3S, 4S) forms. The invention extends to each of these forms including racemates.

It should also be appreciated that potassium channel activators such as those herein described, in particular cromakalim, attenuate the effects of μ-receptor antagonists such as morphine. The present invention therefore extends to the co-administration of a potassium channel activator and a μ-receptor antagonist for treating pain in mammals, such as humans.

The administration of the potassium channel activator may be by way of oral, sublingual, transdermal or parenteral administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the potassium channel activator, such a compound of formula (I) or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more

usually 1 to 3 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.5 to 10 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

Within the above indicated dosage range, no adverse toxicological effects are indicated with potassium channel activators in the method of treatment according to the invention.

For oral or parenteral administration, it is greatly preferred that the potassium channel activator is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol;

preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if a desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the potassium channel activator and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

The present invention also provides the use of a potassium channel activator, such as a compound of formula (I) or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of pain in mammals such as humans. Such treatment and/or prophylaxis may be carried out as hereinbefore described.

The present invention further provides a pharmaceutical composition for use in the treatment of pain which comprises a potassium channel activator, such as or a compound of formula (I) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

Types of pain that are particularly suitable for treatment by potassium channel activators such as or a compound of formula (I) or a pharmaceutically acceptable salt thereof, include pain associated with inflammation (such as arthritis) and peripheral diabetic neuropathy, the stump pain associated with amputation, and the pain associated with cancer.

Such compositions may be prepared in the manner as hereinbefore described.

The following pharmacological data illustrates the present invention.

Pharmacological Data

**Method 1**

**Facilitation of the tail-flick reflex by noxious cutaneous stimulation in the rat**

R. A. Cridland and J. L. Henry, Brain Res.462 (1988)15-21.

**MATERIALS AND METHODS**

**Anaesthesia**

Experiments were done on lightly anaesthetised male Sprague-Dawley rats (250-350g). Anaesthesia was induced by an i.p. injection of a solution of sodium pentobarbital (20mg/kg).

**Measurement of reaction time in the tail flick test**

To elicit the tail withdrawal reflex, the tail was placed above a projector bulb which was focussed 10-12cm proximal to the tip of the tail. A flick of the tail exposed the light beam to a photodetector which in turn stopped the beam and was linked to a timer displaying the reaction time, measured to within one hundredth of a second. Reaction time to tail withdrawal was measured at 3 min intervals. Three successive readings were taken to establish the baseline reaction time. The experiment was not continued unless these three reaction times had a standard deviation of less than 10% of the mean. The intensity of the bulb was set so that the baseline reaction time was a few seconds and was not adjusted thereafter. Trials were terminated automatically if a tail flick did not occur within 10 seconds.

**Prolonged noxious cutaneous stimulation by tail immersion**

After 3 readings were taken to establish the baseline reaction time, intense noxious stimulation was applied to the tail by immersing the distal 4cm in water maintained at 55±1°C for 1.5min. There was usually an initial withdrawal reflex but this subsided rapidly so that the tail remained flaccid in the water for the remainder of the immersion period. Immersion was timed to end 0.5min prior to the next test for reaction time. Four more readings were then taken and the animal was sacrificed. In

a group of animals (±)trans-3,4-dihydro-2,2-dimethyl-4-(2-oxo-piperidin-1-yl)-2H-pyrano[3,2-c]pyridin-3-ol (HT 44033)(10mg/kg) was administered s.c. 20 mins prior to establishing the mean baseline reaction time and the experiment was carried out as above.

**Results**

The following graph was obtained showing that the compound clearly attenuated the effects of tail-immersion on reaction time.

**Method 2**

**Para-phenylquinone-induced abdominal writhing test in mice**

The methodology employed is based on that described by Sigmund et al, Proc. Soc. Exptl. Biol. 95, 729/1957, modified by Milne and Twomey, Agents and Actions, 10, 31/1980.

Male Charles River mice (Swiss Strain), 20-35g body weight, are used. Animals are allowed food and water **ad libitum** and are randomized into groups of 10 prior to experimentation. Test compounds are dissolved in either distilled water or distilled water plus 0.1 M AMS, and administered by the subcutaneous route in a final volume of 10 ml/Kg. Control animals receive 10 ml/Kg of the appropriate vehicle alone. Following a pretreatment period of 20 min., mice are injected intraperitoneally with p-phenylquinone, 2 mg/Kg at 37°C in a final volume of 10 mg/Kg. The mice are then placed, in groups of 3, in a compartmented perspex box maintained at room temperature and are observed for a period of 8 min. During this period the number of abdominal writhing responses per animal are recorded where writhing consists of an intermittent contraction of the abdomen associated with hind leg extension.

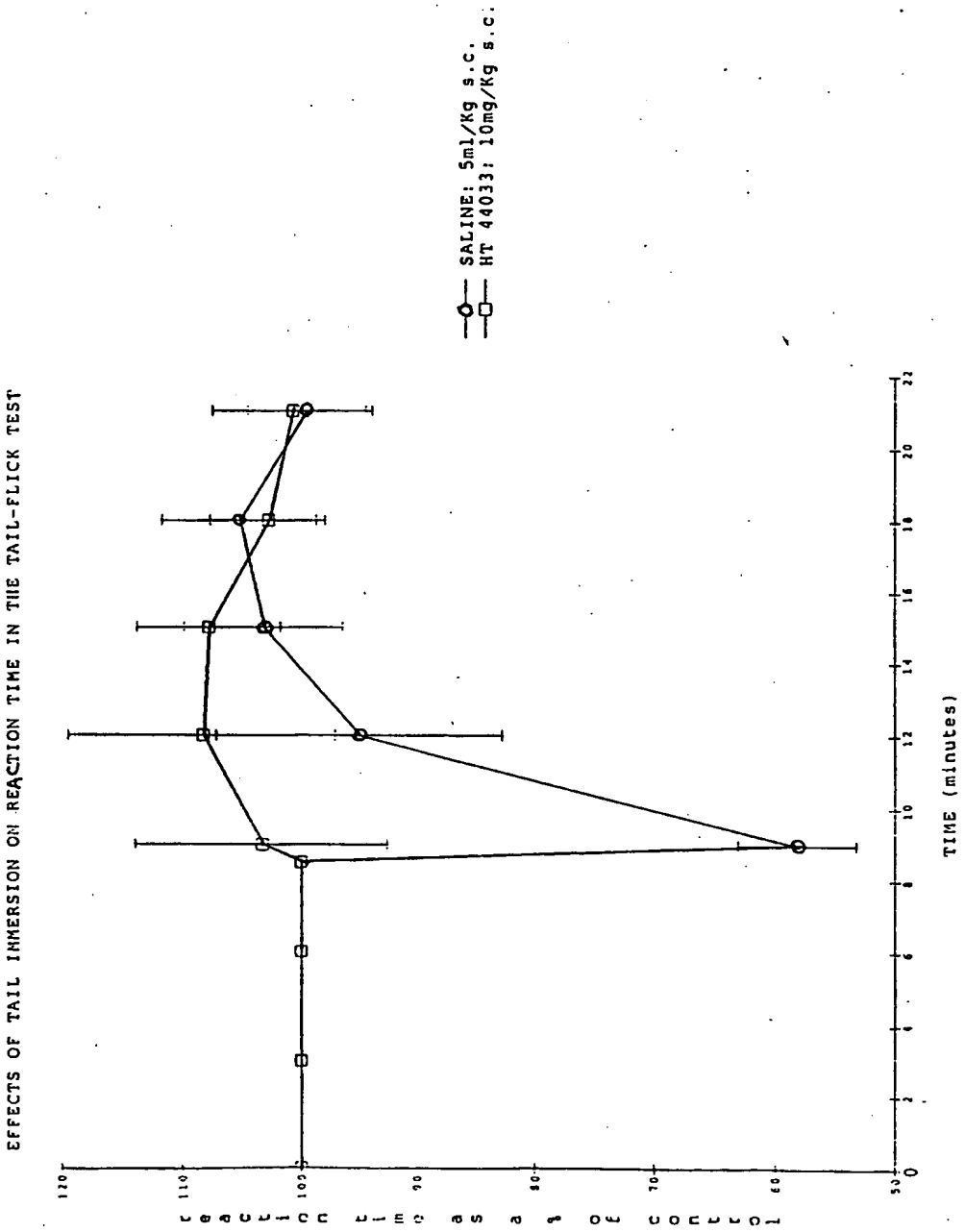
The degree of antinociceptive protection afforded by a test compound is determined as the mean number of writhing responses observed in the treated group (T) expressed as a percentage of the mean number of writhing responses in the control group (C) according to the following formula:

$$1-\frac{T}{C} \times 100\% = \%\ \text{graded protection}$$

**Results**

Cromakalim has an $ED_{50}$ of 15 mg/kg s.c. in the above test.

Levcromakalin has an $ED_{50}$ of 13 mg/kg s.c. in the above test.
Pinacidil 30 mg/kg s.c. = 53%


EFFECTS OF TAIL IMMERSION ON REACTION TIME IN THE TAIL-FLICK TEST
SALINE: 5ml/Kg s.c.
HT 44033: 10mg/Kg s.c.
TIME (minutes)
0
2
4
6
8
10
12
14
16
18
20
22
50
60
70
80
90
100
110
120

**Method 3**

**Antinociception**

**Tail-flick test in mice**

The methodology employed is based on that described by D'Amour and Smith, J. Pharmacol. Exp. Ther. 72, 74 (1941).

Male Charles River mice (Swiss Strain) 29-35 g body weight are used.

Animals are allowed food and water *ad libitum* and are randomized into groups of 10 prior to experimentation. Before administration of the test compound, the reaction time of each animal is determined by focusing a beam of light onto the tail, eliciting a reflex withdrawal after a certain latency; only mice exhibiting a latency between 3-8 sec. are used subsequently in the evaluation of drug effects.

Test compounds are dissolved in either distilled water of distilled water plus 0.1M AMS and administered by the intrathecal route in a final volume of 5 µl/mouse, according to the method described by Hylden and Wilcox, Eur. J. Pharmacol. 67, 313 (1980).

Four hours prior the beginning of experiments, mice are anaesthetized with pentobarbital (80mg/Kg i.p.) and a caudal cutaneous incision (1 cm) is performed on the back using a disposable 30 gauge 1/2 inch needles mated to a 50 µl luer siringe d(Hamilton). The drug are delivered intrathecally between L5 and L6 of spinous process.

Control animals receive 5 µl/mouse of the appropriate vehicle alone. Following a pretreatment period of 10 min., the mice are again placed under the heat source and the rection time re-determined.

Percentage quantal protection is determined as the number of mice in which the reaction time is doubled compared to pretreatment values, expressed as a apercentage of the total number of mice in the group.

**Results**

**Interaction between Morphine and Cromakalim**

| nº animals | Compound | Dose mg.Kg -1 s.c. | Mouse Tail-flick | |
|---|---|---|---|---|
| | | | Protected / Treated | ED50 e C.L. mg.Kg -1 s.c. |
| 10 | Morphine | 1.5 | 3/10 | |
| 10 | Morphine | 3.0 | 6/10 | 2.24±(1.51-3.33) |
| 10 | Morphine | 6.0 | 10/10 | |
| 10 | Morphine + Cromakalim | 0.75 + 1 | 2/10 | |
| 10 | Morphine + Cromakalim | 1.5 + 1 | 5/10 | 1.36+(0.91-2.04) |
| 10 | Morphine + Cromakalim | 3.0 + 1 | 9/10 | |

## Claims

1. A method for the treatment of pain in mammals, which comprises administering to the mammal in need of such treatment an effective amount of a potassium channel activator.

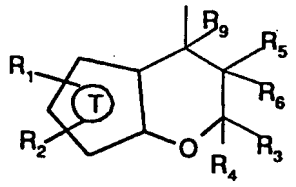
2. A method according to claim 1 in which the potasium channel activator is a compound of formula (I), or a pharmaceutically acceptable salt thereof:

(I)

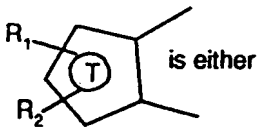
wherein:

P is a ring system selected from the following:

a)

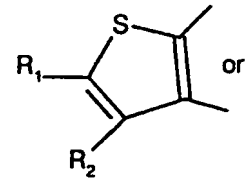


wherein;



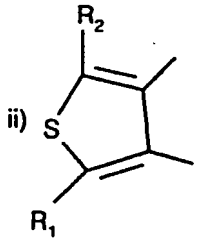
is either

i)



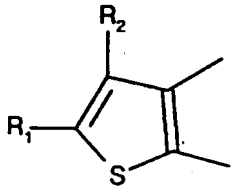
or

ii)



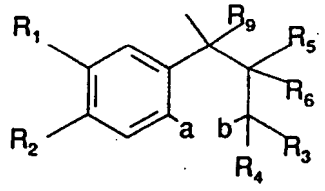
or

iii)

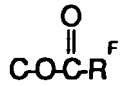


and the other variables are as defined below:

b)

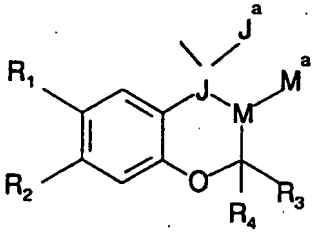


in which either a and b together represent a bond or $CH_2$ or a and b together represent a carbonyl group, a group C=NOR$^F$, CHOR$^F$ or



where R$^F$ is hydrogen or $C_{1-6}$ alkyl; or

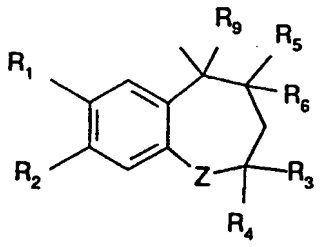
c)



in which either J is nitrogen and J$^a$ is a lone pair of electrons, M is carbon and M$^a$ is $R_5$; or

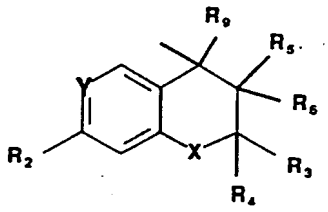
J is carbon and M is nitrogen and J$^a$ and M$^a$ are hydrogen; or

d)



in which Z is oxygen or $CH_2$;

e)



in which X is oxygen or NR in which R is hydrogen or $C_{1-4}$ alkyl; Y is

nitrogen and $R_2$ is hydrogen or Y is C-$R_1$;

and;

where:
either one of $R_1$ and $R_2$ is hydrogen and the other is selected from the class of hydrogen, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyl optionally interrupted by oxygen or substituted by hydroxy, $C_{1-6}$ alkoxy or substituted aminocarbonyl, $C_{1-6}$ alkylcarbonyl, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ alkylcarbonyloxy, $C_{1-6}$ alkoxy, nitro, cyano, halo, trifluoromethyl, $CF_3S$, or a group $CF_3$-A-, where A is -$CF_2$-, -CO-, -$CH_2$-, CH(OH), $SO_2$, SO, $CH_2$-O, or CONH, or a group $CF_2H$-A'- where A' is oxygen, sulphur, SO, $SO_2$, $CF_2$ or CFH; trifluoromethoxy, $C_{1-6}$ alkylsulphinyl, perfluoro $C_{2-6}$ alkylsulphonyl, $C_{1-6}$ alkylsulphonyl, $C_{1-6}$ alkoxysulphinyl, $C_{1-6}$ alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, phosphono, arylcarbonyloxy, heteroarylcarbonyloxy, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, $C_{1-6}$ alkylcarbonylamino, $C_{1-6}$ alkoxycarbonylamino, $C_{1-6}$ alkyl-thiocarbonyl, $C_{1-6}$ alkoxy-thiocarbonyl, $C_{1-6}$ alkyl-thiocarbonyloxy, 1-mercapto $C_{2-7}$ alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two $C_{1-6}$ alkyl groups, or $C_{1-6}$ alkylsulphinylamino, $C_{1-6}$ alkylsulphonylamino,$C_{1-6}$ alkoxysulphinylamino or $C_{1-6}$ alkoxysulphonylamino, or ethylenyl terminally substituted by $C_{1-6}$ alkylcarbonyl, nitro or cyano, or -C($C_{1-6}$ alkyl)NOH or -C($C_{1-6}$ alkyl)$NNH_2$, or one of $R_1$ and $R_2$ is nitro, cyano or $C_{1-3}$ alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two $C_{1-6}$ alkyl or by $C_{2-7}$ alkanoyl; or where possible $R_1$ and $R_2$ when adjacent together are -$(CH_2)_4$- or -CH = CH-CH = CH-, or form an optionally substituted triazole or oxadiazole ring;
one of $R_3$ and $R_4$ is hydrogen or $C_{1-4}$ alkyl and the other is $C_{1-4}$ alkyl, $CF_3$ or $CH_2X^a$ where $X^a$ is fluoro, chloro, bromo, iodo, $C_{1-4}$ alkoxy, hydroxy, $C_{1-4}$ alkylcarbonyloxy, -S-$C_{1-4}$ alkyl, nitro, amino optionally substituted by one or two $C_{1-4}$ alkyl groups; cyano or $C_{1-4}$ alkoxycarbonyl or $R_3$ and $R_4$ together are $C_{2-5}$ polymethylene optionally substituted by $C_{1-4}$ alkyl;
$R_5$ is $C_{1-6}$ alkylcarbonyloxy, benzoyloxy, $ONO_2$, benzyloxy, phenyloxy or $C_{1-6}$ alkoxy and $R_6$ and $R_9$ are hydrogen or $R_5$ is hydroxy and $R_6$ is hydrogen or $C_{1-2}$ alkyl and $R_9$ is hydrogen or $R_5$ together with $R_9$ represents a bond and $R_6$ is hydrogen or $R_6$ and $R_9$ represents a bond and $R_5$ is hydroxy;
$R_7$ is a group of structure i):

(i)

wherein

either X is oxygen or sulphur; and

$R_7'$ is hydrogen, $C_{1-6}$ alkyl optionally substituted by hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl or carboxy, $C_{1-6}$ alkyl substituted by halogen, or $C_{2-6}$ alkenyl; aryl or heteroaryl either being optionally substituted by one or more groups or atoms selected from the class of $CF_3$, $CF_3O$-, $C_{1-6}$ alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, $C_{1-12}$ carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two $C_{1-6}$ alkyl groups; and

$R_8$ is hydrogen, $C_{1-6}$ alkyl, or a group $OR_p$ or $NHCOR_q$ wherein $R_p$ is hydrogen, $C_{1-6}$ alkyl, aralkyl, $C_{1-7}$ alkanoyl or aroyl and $R_q$ is as defined above for $R_7'$; or

$R_7$ and $R_8$ are joined together to form $C_{3-4}$ polymethylene optionally substituted by one or two $C_{1-6}$ alkyl groups or hydroxy $C_{1-6}$ alkyl, or $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are integers 0 to 2 such that m+n is 1 or 2 and Z is oxygen, sulphur or $NR_9$ wherein $R_9$ is hydrogen, $C_{1-9}$ alkyl, $C_{2-7}$ alkanoyl, phenyl $C_{1-4}$ alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy or halogen; mono- or bi-cyclic heteroarylcarbonyl; or $R_7$ and $R_8$ are joined to form $-B^1=B^2-B^3=B^4-$ wherein one of $B^1$ to $B^4$ is $CR_r$ or N and the other three are $CR_r$ wherein $R_r$ is hydrogen or $C_{1-6}$ alkyl;

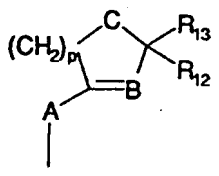
or X is N-CN, N-$NO_2$, N-$COR_{10}$ or N-$SO_2R_{10}$ wherein $R_{10}$ is $C_{1-3}$ alkyl, $NH_2$, $NH(C_{1-3}$ alkyl), $CF_3$ or phenyl optionally substituted as defined for $R_x$; and

$R_7'$ is $NHR_{11}$ wherein $R_{11}$ is hydrogen, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl; and

$R_8$ is hydrogen or $C_{1-6}$ alkyl; or

$R_7'$ and $R_8$ together are $C_{2-4}$ polymethylene;

or $R_7$ is a group of structure ii):



(ii)

wherein

A is O or $NR_{14}$ wherein $R_{14}$ is hydrogen, $C_{1-4}$ alkyl, formyl, acetyl or hydroxymethyl;

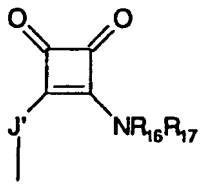
B is N or $CR_{15}$ wherein $R_{15}$ is hydrogen, halogen, formyl or hydroxymethyl:

C is $CH_2$, O, S, CH-Halogen, amino or $C_{1-6}$ alkylamino;

p is 1, 2 or 3; and

$R_{12}$ and $R_{13}$ are independently hydrogen or methyl or together are oxo- or thia-;

or $R_7$ is a group of structure iii)

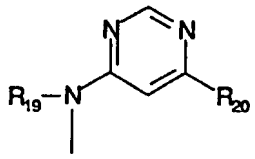


(iii)

wherein

J' is O or $NR_{18}$ wherein $R_{18}$ is hydrogen or $C_{1-6}$ alkyl, and $R_{16}$ and $R_{17}$ are independently hydrogen, $C_{1-6}$ alkyl, or (when $R_{16}$ is hydrogen) then $R_{17}$ is allyl, propargyl or $C_{3-6}$ cycloalkyl;

or $R_7$ is a group of structure iv)

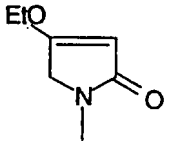


(iv)

wherein

$R_{19}$ is hydrogen or $C_{1-6}$ alkyl; and $R_{20}$ is halo, amino or methylamino;

or $R_7$ is, or formula v);



(v)

or $R_7$ is tetrahydroisoquinolinone, 2,3-dihydro-1H- isoindol-1-one, 2-pyridine

N-oxide, 2-hydroxyphenyl or 2-hydroxypyridine (all four possible isomers); the $R_7$ moiety being cis or trans to the $R_5$ group when $R_5$ is other than hydrogen or a bond.

3. A method according to claim 1 in which P is selected from e).

4. A method according to claim 2 or 3 in which Y is nitrogen and $R_2$ is hydrogen.

5. A method according to claim 2 or 3 in which Y is C-$R_1$ and $R_2$ is hydrogen.

6. A method according to claim 5 in which $R_1$ is cyano.

7. A method according to any one of claims 2 to 6 in which $R_3$ and $R_4$ are both methyl.

8. A method according to any one of claims 2 to 7 in which $R_5$ is hydroxy and $R_6$ and $R_9$ are both hydrogen.

9. A method according to any one of claims 2 to 8 in which X is oxygen.

10. A method according to any one of claims 2 to 9 in which $R_7$ is selected from i).

11. A method according to claim 10 in which $R_7$ is 2-oxo-1-pyrrolidinyl or 2-oxo-1-piperidinyl.

12. A method according to claim 1 or 2 in which the potassium channel activator is (±)*trans*-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-2H-pyrano-[3,2-c]pyridin-3-ol.

13. A method according to claim 1 or 2 in which the potassium channel activator is (±)-6-cyano-3,4-dihydro-2,2-dimethyl-*trans*-4-(2-oxo-1-pyrrolidinyl)-2H-benzo[b]pyran-3-ol.

14. A method according to claim 1 or 2 in which the potassium channel activator is RO 316930, SDZ PCO-400, WAY-120491, HOE-234, HOE-231, S-0121, FR 119748, EMD 57283, YM 934, NIP-121, RWJ-29009, BRL 55834, BDF 9333, U-89, 232, KP294, SR 47063, Y27152, Y26763, UR 8225, KC-399, LP805, KRN 2391 and

nicorandil.

15. A method of treating pain in mammals comprising the co-administration to the sufferer in need thereof, a μ-receptor antagonist and a potassium channel activator.

16. A method according to claim 15 in which the μ-receptor antagonist is morphine.

17. A method according to claim 15 or 16 in which the potassium channel activator is cromakalim or levcromakalim.

18. The use of a potassium channel activator in the manufacture of a medicament for the treatment of pain in mammals.

19. A pharmaceutical composition for use in the treatment of pain which comprises a potassium channel activator and a pharmaceutically acceptable carrier.